American Journal of Epidemiology

Vol. 157, No. 3
Printed in U.S.A.
DOI: 10.1093/aje/kwf189

Mortality from Diseases of the Circulatory System in Radiologic Technologists in the United States

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Received for publication June 7, 2002; accepted for publication August 28, 2002.

Although increased mortality from diseases of the circulatory system has been observed in patients treated with radiotherapy, the effects of chronic low-dose radiation exposure are not clear. Among 90,284 US radiologic technologists who responded to a mailed questionnaire during 1983–1989, the authors evaluated mortality from circulatory system diseases through 1997 in relation to job history and work procedures as surrogates for radiation exposure. They used Poisson regression models stratified for sex, race, age, and calendar year and adjusted for smoking, body mass index, alcohol intake, marital status, parity, menopausal status, and history of myocardial infarction. A total of 1,107,100 person-years accrued, and 1,070 subjects died from circulatory system diseases. Relative risks for first employment during 1950–1959, 1940–1949, or before 1940, compared with 1960 and later, were 1.01 (95% confidence interval (CI): 0.78, 1.30), 1.14 (95% CI: 0.86, 1.50), and 1.42 (95% CI: 1.04, 1.94), respectively (trend $p < 0.001$). For the subset of deaths from cerebrovascular disease ($n = 174$), the respective relative risks were 0.90 (95% CI: 0.45, 1.78), 1.54 (95% CI: 0.74, 3.23), and 2.40 (95% CI: 1.09, 5.31) (trend $p = 0.004$), and for deaths from ischemic heart disease ($n = 633$), the relative risks were 0.98 (95% CI: 0.71, 1.35), 1.00 (95% CI: 0.71, 1.42), and 1.22 (95% CI: 0.81, 1.82) (trend $p = 0.026$). The relative risks for mortality from circulatory system diseases and the subset of cerebrovascular disease increased significantly with the number of years worked before 1950 (trend $p = 0.007$ and < 0.001, respectively). The data suggest increased mortality from diseases of the circulatory system with occupational radiation exposure before 1950 when radiation doses were likely high.

cerebrovascular disorders; cohort studies; medical staff; mortality; myocardial ischemia; radiation

Abbreviation: CI, confidence interval.

Although the carcinogenic effect of radiation is well known, there is emerging evidence that diseases of the circulatory system occur as a late consequence of radiation exposure. High-dose mediastinal irradiation administered to patients with Hodgkin's disease or breast cancer has been reported to induce delayed cardiovascular disease (1–3). More recently, studies of the survivors of the 1945 atomic bombings in Japan have provided convincing evidence that excess risk of stroke and heart disease can be induced by exposure to radiation at a level much lower than that given in radiotherapy, although the excess risk, in relative terms, is smaller compared with that of cancer (4). Radiation is widely used in medicine, ranging from cancer radiotherapy and interventional radiology, which exposes a small number of patients to high doses of radiation, to low-dose diagnostic procedures applied to a large number of patients. Even though the risk for diseases of the circulatory system due to low levels of radiation exposure may be small, common exposures to low levels of radiation may raise a public health concern. Epidemiologic data on low-dose irradiated populations are scarce and conflicting: An increased cardiovascular disease risk was reported from studies of early radiologists in the United States (5) but not from radiologists in the United Kingdom (6). The conflicting results may be due to the fact that not all of these studies accounted for the potentially confounding effects of known risk factors for diseases of the circulatory system.

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We present results from a nationwide ongoing follow-up investigation of US radiologic technologists certified between 1926 and 1982 (7). For this cohort, we have data available on mortality, individual work histories (to characterize occupational radiation exposure), and known risk factors for diseases of the circulatory system. These data enabled us to carry out detailed analyses of mortality from circulatory system diseases in relation to radiation exposure, accounting for potential confounding by known risk factors.

MATERIALS AND METHODS

Cohort design and follow-up

The cohort was established to study cancer and other health effects of chronic exposure to radiation in radiologic technologists. Details of the study population and methods are provided elsewhere (7). In brief, the initial cohort included 146,022 radiologic technologists (73 percent female) who were certified by the American Registry of Radiologic Technologists for 2 years or longer during 1926–1982 and resided in the United States. During 1983–1989, all subjects located alive (n = 132,519 or 91 percent) were mailed a detailed questionnaire including questions on work history and practices, medical history, lifestyle characteristics, and established or suspected cancer risk factors (8). Questionnaire respondents were followed to ascertain vital status and cause of death for those who died from the date of questionnaire completion (1983–1990) through the end of 1997. Active registrants of the American Registry of Radiologic Technologists were followed through annual certification renewals, while inactive registrants were followed through linkage with various databases including Social Security Administration files, motor vehicle bureau records, Health Care Financing Administration records, the National Death Index, and state mortality records. Death certificates were obtained for decedents, and underlying causes of death were coded according to the *International Classification of Diseases*. No attempt was made to validate cause-of-death information using medical records.

The present analysis was based on the subset of 90,284 questionnaire respondents (68 percent response rate), including 69,511 women. We evaluated the year each subject first worked as a radiologic technologist, the duration of employment, and known risk factors for diseases of the circulatory system (education, cigarette smoking, alcohol consumption, body mass index, history of myocardial infarction, marital status, parity, age at menarche, menopausal status including surgical menopause, age at menopause, hormone replacement therapy, and use of oral contraceptives). The risk factors examined were considered potential confounders in the evaluation of the effect of radiation exposure.

Radiation exposure

Because individual radiation dose estimates were not available, we used self-reported work history data, that is, year first worked as a radiologic technologist and number of years worked in specific time periods, to construct proxy measures for characterizing the level of radiation exposure. This strategy takes into account the historical changes in radiation exposure. Radiation safety standards have improved markedly over the decades during which the cohort subjects worked, resulting in a reduction of occupational radiation exposure. The first formal standard proposed in 1934 was 0.1 roentgen per day (about 0.3 Sv per year, 1 year = 300 work days)—about half of what had previously been considered "tolerant" (9). A limit of 0.15 Sv per year was adopted by the International Commission of Radiological Protection in early 1950 (9), and in 1957, the Commission recommended an occupational dose limit of 0.05 Sv per year, which largely remained unchanged until 1993 (9). Therefore, levels of exposure before 1950 may have been 6–12 times higher compared with more recent time periods, that is, 1980 or later.

Working specifically with fluoroscopy, multifilm, routine x-ray examinations, and radioisotope treatment may have increased radiation exposure (10), but most cohort members worked with several or all of these procedures including fluoroscopy (90.4 percent), multifilm (87.3 percent), routine x-ray examinations (88.3 percent), and radioisotope treatment (90.3 percent). This precluded separate evaluation of worker subgroups, where each performed a specific procedure.

Statistical analysis

Person-years were compiled according to sex, race (White, non-White), age (0–24, 25–29, ..., 75–79, ≥80 years), and calendar year (1980–1984, 1985–1989, 1990–1994, 1995–1998) from the date of questionnaire completion (1983–1990) through the end of 1997, the date of death, or the date of loss to follow-up, whichever came first. For subjects lost to follow-up, person-year accumulation ceased at the last date known alive. When there was an unknown date of death or when personal information to search the National Death Index was missing, subjects were considered lost to follow-up at their last date known alive. For subjects with an unknown cause of death, the person-year accumulation ceased at the date of death, but subjects did not contribute cases to any specific cause of death category except all causes of death.

Relative risks for mortality from diseases of the circulatory system and the subgroups of ischemic heart disease and cerebrovascular disease were estimated using log-linear Poisson regression models (11). The background risk was estimated using internal comparisons (the background risk estimated nonparametrically within the cohort using models stratified by calendar year, age, sex, and race) and external comparisons (the background risk assumed to be proportional to year-, age-, sex-, and race-specific US mortality rates). External comparisons were performed to evaluate the influence of secular trends on the internal comparisons. The year first worked and the number of years worked were found to be correlated with attained age and calendar year; mortality rates for diseases of the circulatory system are known to vary with age and calendar year (12). This can induce intrinsic confounding leading to collinearity in extreme situations. External comparisons can be useful in such situations because the background risk is taken from population data rather than being estimated from the cohort, although the assumption is that the background mortality in the cohort is proportional to that in the general population. (For a general description of the use of external rates, see reference 11, p. 151.)

The year first worked and the number of years worked were analyzed together in a multivariate model. Analyses of the number of years worked in different time periods were restricted to subjects between 15 and 65 years of age (and therefore eligible for employment) in the respective time period and were adjusted for the years worked in other time periods. We evaluated separately and combined the potential confounding effects of education, cigarette smoking, alcohol consumption, body mass index, history of myocardial infarction, marital status, parity, age at menarche, menopausal status, age at menopause, hormone replacement therapy, and use of oral contraceptives. Missing data were coded as a separate category (estimates not shown).

We used 95 percent Wald-based confidence intervals. Tests of trend for categorical variables were tests of the slope of the corresponding continuous variable. Effect modification was evaluated on the basis of improvement of model fit quantified by the likelihood ratio test statistic. All tests were two sided at the 5 percent significance level. EPICURE software was used for all analyses (13).

Ethical standards

This study is approved annually by the National Cancer Institute Special Studies Institutional Review Board of Research Involving Human Subjects (protocol no. OH97-C-N053). Participants were informed of the objectives, procedures, and voluntary nature of the study in the cover letter to the questionnaire. Informed consent to participate in the study was obtained through completion and return of the questionnaire. Consent to access medical records was obtained with a separate signed consent form.

RESULTS

Of the 90,284 questionnaire respondents (20,773 male, 69,511 female), 82,492 subjects were alive at the end of follow-up on December 31, 1997; 3,562 subjects had a known date of death (known cause for 3,396), and 4,230 subjects were lost to follow-up. The loss to follow-up resulted in only 2,570 person-years lost, that is, 0.2 percent of all person-years of follow-up, since 85 percent of the subjects lost were lost within 1 year of the end of follow-up.

The reasons for loss to follow-up were insufficient personal information to search the National Death Index (4,160 subjects), unknown date of death (69 subjects), or other (one subject). The median follow-up from questionnaire completion to study end was 13 years, with 1,107,100 person-years accrued. Table 1 shows the causes of death among the deceased cohort members. Almost as many men (n = 510) as women (n = 560) died of circulatory system diseases, although men constituted only 23 percent of the questionnaire respondents.

The majority of questionnaire respondents were born between 1935 and 1955 (66 percent), began working as a radiologic technologist between 1955 and 1975 (67 percent), and were 25 years of age or less when first employed (80 percent) (table 2). At questionnaire completion, the average age was 38 years, the majority were married (75 percent), and females were mostly premenopausal (77 percent) and had at least one livebirth (65 percent). About 50 percent of the subjects smoked cigarettes, and about 3 percent of the males (n = 702) and less than 1 percent of the females (n = 505) reported a history of myocardial infarction (data not shown).

Table 3 shows relative risks for potential confounders that were significantly associated with mortality from circulatory system diseases in univariate models and in multivariate models that included all other significant variables. For all circulatory system diseases, unmarried status was a weak risk factor; obesity (body mass index, >28), long smoking duration, and early menopause were moderate risk factors; and a history of an early myocardial infarction was a strong risk factor. Moderate alcohol consumption and a history of livebirths were protective. Subjects with ischemic heart disease (n = 633) had a pattern similar to that of the entire group with circulatory system diseases (n = 1, 070). For subjects with cerebrovascular disease (n = 174), confidence intervals were much wider because of the smaller number of cases, and relative risks were only moderately elevated.

Table 4 shows relative risks according to the year first worked and the number of years worked, adjusted for potential confounders. For all circulatory system diseases, relative risks based on internal comparisons increased with earlier year first worked and attained statistical significance for year first worked before 1940 compared with 1960 or later (relative risk = 1.42, 95 percent confidence interval (CI): 1.04, 1.94; trend $p < 0.001$). For the subgroup with ischemic heart disease, the pattern was similar but less pronounced for year first worked (trend $p = 0.026$). For cerebrovascular disease, higher relative risks were seen for earlier year first worked. Subjects who began working before 1940 had a relative risk based on internal comparisons of 2.40 (95 percent CI: 1.09, 5.31) compared with subjects who first worked in 1960 or later (trend $p = 0.004$). There was no association with the cumulative number of years worked for any of the disease categories. Adjusting for potential confounders slightly increased the risk estimates for the year first worked and the number of years worked.

For those dying of hemorrhagic stroke (n = 63), the relative risks based on internal comparisons for the year first worked in 1950–1959, in 1940–1949, and before 1940, compared with 1960 or later, were 1.04 (13 cases), 2.02 (17 cases), and 2.17 (nine cases), respectively, with a nonsignificant trend ($p > 0.5$). For those dying of nonhemorrhagic stroke (n = 24), the respective relative risks were 0.70 (three cases), 0.49 (three cases), and 3.71 (12 cases), with a significant trend ($p = 0.011$). For unspecified stroke (n = 87), the respective relative risks were 0.82 (11 cases), 1.51 (34 cases), and 1.96 (31 cases), with a significant trend ($p = 0.023$). No relation was found with the cumulative number of years worked among workers in the three subgroups of stroke.

TABLE 1. Distribution of causes of death in deceased members of the cohort of certified US radiologic technologists who completed a questionnaire between 1983 and 1990 and were followed from completion of the questionnaire through the end of 1997

	Males		Females	
	No.	%	No.	%
Infectious and parasitic diseases*	95	6.6	30	1.4
Malignant neoplasms†	412	28.6	901	42.5
Diseases of the circulatory system‡	510	35.4	560	26.4
Ischemic heart disease§	343	23.8	290	13.7
Cerebrovascular disease¶	59	4.1	115	5.4
Other diseases of the circulatory system	108	7.5	155	7.3
Diseases of the respiratory system#	98	6.8	151	7.1
Diseases of the digestive system**	41	2.8	64	3.0
Diseases of the genitourinary system††	17	1.2	17	0.8
Injuries and poisoning‡‡	99	6.9	118	5.6
All other causes	106	7.4	177	8.4
Unknown causes	64	4.4	102	4.8
All deceased	1,442	100.0	2,120	100.0

* *International Classification of Diseases*, Eighth Revision (ICD-8), codes 000.0–136.9; *International Classification of Diseases*, Ninth Revision (ICD-9), codes 001.0–139.9.
† ICD-8 codes 140.0–209.9; ICD-9 codes 140.0–208.9, 238.4, 238.6, and 289.8.
‡ ICD-8 codes 390.0–458.9; ICD-9 codes 390.0–459.9.
§ ICD-8 and ICD-9 codes 410.0–414.9.
¶ ICD-8 and ICD-9 codes 430.0–438.9.
# ICD-8 and ICD-9 codes 460.0–519.9.
** ICD-8 codes 520.0–577.9; ICD-9 codes 520.0–579.9.
†† ICD-8 and ICD-9 codes 580.0–629.9.
‡‡ ICD-8 and ICD-9 codes 800.0–999.9.

Because of higher doses of ionizing radiation in the earlier calendar time periods, the cumulative years worked, excluding consideration of the decades worked, may not be a good surrogate for cumulative exposure. Table 5 shows the estimated relative risks according to the number of years worked in different time intervals. For diseases of the circulatory system, the relative risks based on internal comparisons increased with the number of years worked prior to 1950 (based on 853 cases, trend $p = 0.007$), when exposure to ionizing radiation was substantially higher, but not in more recent time intervals. For cerebrovascular disease, but not for ischemic heart disease, the risk rose significantly with the number of years worked before 1950: Relative risks based on internal comparisons were 1.48 (32 cases) and 2.01 (74 cases) for working up to 5 years and more than 5 years before 1950, respectively, compared with not working before 1950 (31 cases), adjusted for the number of years worked in other time intervals (trend $p < 0.001$).

Results were generally similar for external and internal comparisons. Almost identical increased risks were found for cerebrovascular disease (tables 4 and 5). For those who died of ischemic heart disease, risks based on external comparisons were somewhat lower for the year first worked, in particular among those first employed prior to 1940.

We evaluated whether the associations found differed by gender, age, race, or history of myocardial infarction. The risk estimates did not differ statistically or substantively by gender, age, and race. However, the increase in risk for all circulatory system diseases with earlier year first worked was restricted to subjects with no prior myocardial infarction (808 cases, data not shown).

DISCUSSION

We found an increased mortality risk for circulatory system diseases among radiologic technologists who first worked earlier than 1950 compared with 1960 or later. Increasing relative risks for circulatory system diseases and, especially pronounced, for cerebrovascular disease were found with the number of years worked before 1950. These findings are consistent with an increased mortality risk from circulatory system diseases, especially stroke, associated with chronic low-dose radiation exposure.

Our findings with respect to potential confounders were consistent with the literature. The data showed an increased mortality risk from circulatory system diseases associated with smoking (14, 15), a protective effect from moderate but not high alcohol consumption (16), and an increased risk in postmenopausal women (17). The reduced mortality risk from circulatory system diseases in parous women was unexpected and may be due to chance.

TABLE 2. Demographic characteristics of the subcohort of certified US radiologic technologists who completed a questionnaire between 1983 and 1990 and were followed from completion of the questionnaire through the end of 1997

Demographic characteristic	Males		Females	
	No.	%	No.	%
Race				
White	18,296	88.1	66,054	95.0
Non-White	2,477	11.9	3,457	5.0
Year of birth				
Before 1935	4,090	19.7	8,080	11.6
1935–1944	4,553	21.9	14,201	20.4
1945–1954	9,575	46.1	31,601	45.5
1955 and later	2,555	12.3	15,629	22.5
Age (years) at entry into the cohort				
≤30	2,544	12.3	15,883	22.9
31–35	4,914	23.7	17,801	25.6
36–40	4,399	21.2	13,464	19.4
41–45	2,808	13.5	8,735	12.6
>45	6,108	29.4	13,628	19.6
Duration of follow-up (years)				
≤10	5,998	28.9	14,126	20.3
11–12	5,756	27.7	17,519	25.2
13–14	9,019	43.4	37,866	54.5
Year first worked as a radiologic technologist				
1955 or before	3,213	15.5	7,936	11.4
1956–1965	4,444	21.4	15,530	22.3
1966–1975	8,861	42.7	31,351	45.1
After 1975	3,512	16.9	12,958	18.6
Never worked	258	1.2	650	0.9
Unknown	485	2.3	1,086	1.6
Age (years) first worked				
≤20	1,904	9.2	22,179	31.9
21–25	10,580	50.9	37,768	54.3
>25	7,546	36.3	7,828	11.3
Never worked	258	1.2	650	0.9
Unknown	485	2.3	1,086	1.6
Total	20,773	100.0	69,511	100.0

Studies of radiologists and radiologic technologists in the United States (7, 18), the United Kingdom (6), Canada (19), Japan (20), Denmark (21), and China (22), like ours, lacked individual dose estimates. Of these studies, data on the US radiologists showed excess mortality from circulatory system diseases (18), while data on radiologists from the United Kingdom did not (6). Other studies have not provided detailed analyses of diseases of the circulatory system. The radiologist cohort from the United Kingdom included subjects who started working as early as 1897 and therefore likely had higher exposures to ionizing radiation than did the US radiologic technologists. Berrington et al. (6) suggested that the lack of excess mortality from diseases of the circulatory system among radiologists from the United Kingdom may have reflected the healthy worker effect, dose fractionation reducing the risk, or possibly overestimation of doses. Our study, although sharing some of these limitations, differs from the United Kingdom study in individual adjustment for potential confounding factors and evaluating internal comparisons.

Excess heart disease mortality has been linked with high-dose radiation exposure used for treatment of Hodgkin's disease or breast cancer (1, 2). During typical radiotherapy treatments, Hodgkin's disease patients generally received cardiac doses up to 30–35 Sv, and breast cancer patients received tumor doses of 40–50 Sv. Therefore, radiation doses to the heart in these cancer patients were much higher than those likely received by medical radiation workers. The

TABLE 3. Relative risks for mortality and number of cases by selected variables from a multivariate model based on internal comparisons for the subcohort of certified US radiologic technologists who completed a questionnaire between 1983 and 1990 and were followed from completion of the questionnaire through the end of 1997

	Circulatory system diseases*			Ischemic heart disease†			Cerebrovascular disease‡		
	Cases	RR§	95% CI§	Cases	RR	95% CI	Cases	RR	95% CI
Marital status									
Married¶	624	1.00		368	1.00		100	1.00	
Unmarried	420	1.34	1.16, 1.56	247	1.49	1.23, 1.81	68	1.04	0.72, 1.49
Body mass index									
≤28¶	755	1.00		430	1.00		133	1.00	
>28	255	1.56	1.35, 1.80	168	1.71	1.43, 2.05	32	1.29	0.87, 1.91
Ever smoked cigarettes									
No¶	331	1.00		183	1.00		63	1.00	
Yes for ≤20 years	154	1.10	0.90, 1.34	93	1.20	0.92, 1.55	21	0.86	0.52, 1.44
Yes for >20 years	535	1.74	1.50, 2.01	324	1.70	1.40, 2.07	82	1.67	1.17, 2.38
Yes, unknown time	43	1.98	1.44, 2.73	30	2.26	1.53, 3.35	6	1.64	0.70, 3.82
Alcoholic drinks/week									
<1¶	659	1.00		388	1.00		108	1.00	
1–12	330	0.82	0.71, 0.93	195	0.80	0.67, 0.95	53	0.88	0.63, 1.24
>12	61	0.99	0.76, 1.30	38	1.00	0.71, 1.41	9	1.09	0.54, 2.19
No. of livebirths (women)									
0¶	271	1.00		151	1.00		53	1.00	
>0	238	0.82	0.67, 0.99	112	0.74	0.56, 0.97	48	0.74	0.48, 1.15
Menopause (women)									
No¶	75	1.00		25	1.00		25	1.00	
Yes at age ≤50 years	301	1.72	1.19, 2.48	166	1.99	1.14, 3.48	48	0.68	0.31, 1.50
Yes at age >50 years	100	1.47	0.96, 2.24	51	1.56	0.83, 2.92	24	0.82	0.33, 2.03
Yes, unknown age	71	2.57	1.67, 3.97	39	3.00	1.58, 5.68	17	1.42	0.56, 3.57
History of myocardial infarction									
No myocardial infarction¶	808	1.00		441	1.00		146	1.00	
Myocardial infarction at age ≤55 years	133	5.33	4.39, 6.46	102	6.75	5.38, 8.48	12	3.56	1.94, 6.55
Myocardial infarction at age >55 years	89	2.55	2.02, 3.21	64	3.31	2.50, 4.37	8	1.14	0.55, 2.36
Myocardial infarction, unknown age	8	1.78	0.88, 3.60	5	2.10	0.86, 5.11	2	2.07	0,50, 8.62

* *International Classification of Diseases*, Eighth Revision (ICD-8), codes 390.0–458.9; *International Classification of Diseases*, Ninth Revision (ICD-9), codes 390.0–459.9; 1,070 cases.

† ICD-8 and ICD-9 codes 410.0–414.9; 633 cases.

‡ ICD-8 and ICD-9 codes 430.0–438.9; 174 cases.

§ RR, relative risk (stratified for sex, race, attained age, and calendar year of follow-up; missing data were coded as a separate category with estimates not shown); CI, confidence interval.

¶ Baseline category.

only quantitative risk estimates for lower ionizing radiation exposures in relation to circulatory system diseases are from the atomic bomb survivors (4). These can be used to assess whether the doses necessary to achieve the observed risks are compatible with the likely doses received by radiologic technologists, under the simplified assumption that risk does not depend on the instantaneous (atomic bomb survivors) or chronic (radiologic technologists) nature of exposure. Based on the risk estimates per sievert colon dose (a conventionally used measure for the representative dose to internal organs) derived from the data on atomic bomb survivors, the average yearly estimated dose linked with the relative risks for years prior to 1950 found in our study is 0.07 Sv for ischemic heart disease and 0.7 Sv for stroke. The regulatory limit before 1950 was between 0.3 and 0.5 Sv per year. Thus, the estimated dose linked with the relative risk seen in our study for ischemic heart disease, but not for stroke, is well within the regulatory limits. However, the regulatory limits are consistent with an estimated dose (0.3 Sv) linked with a relative risk for stroke at the lower 95 percent confidence limit. For an explanation of the calculations, see the Appendix.

Because routine monitoring of radiation exposure in workplaces was not introduced until early 1950, estimating radiation doses is difficult for subjects who started working

TABLE 4. Relative risks for mortality and number of cases for year first worked and number of years worked in one multivariate model for the subcohort of certified US radiologic technologists who completed a questionnaire between 1983 and 1990 and were followed from completion of the questionnaire through the end of 1997

	Cases	Internal comparison			External comparison		
		RR*	95% CI*	Trend *p*†	RR	95% CI	Trend *p*
Diseases of the circulatory system‡							
Year first worked as a radiologic technologist							
1960 or later§	203	1.00			1.00		
1950–1959	242	1.01	0.78, 1.30		0.92	0.75, 1.12	
1940–1949	351	1.14	0.86, 1.50		1.02	0.83, 1.25	
Before 1940	214	1.42	1.04, 1.94	(<0.001)	1.12	0.89, 1.41	(0.139)
No. of years worked as a radiologic technologist							
≤10§	237	1.00			1.00		
11–20	267	1.03	0.86, 1.23		1.01	0.85, 1.21	
21–30	228	0.96	0.79, 1.16		0.91	0.76, 1.10	
>30	278	0.96	0.79, 1.16	>0.5	0.94	0.78, 1.14	(>0.5)
Ischemic heart disease¶							
Year first worked as a radiologic technologist							
1960 or later§	111	1.00			1.00		
1950–1959	157	0.98	0.71, 1.35		0.97	0.75, 1.26	
1940–1949	214	1.00	0.71, 1.42		0.98	0.75, 1.27	
Before 1940	116	1.22	0.81, 1.82	(0.026)	1.01	0.74, 1.38	(>0.5)
No. of years worked as a radiologic technologist							
≤10§	137	1.00			1.00		
11–20	150	0.96	0.76, 1.21		0.95	0.75, 1.20	
21–30	137	0.89	0.70, 1.14		0.85	0.67, 1.08	
>30	174	0.93	0.72, 1.19	(>0.5)	0.92	0.72, 1.17	(>0.5)
Cerebrovascular disease#							
Year first worked as a radiologic technologist							
1960 or later§	32	1.00			1.00		
1950–1959	27	0.90	0.45, 1.78		0.94	0.54, 1.66	
1940–1949	54	1.54	0.74, 3.23		1.44	0.83, 2.52	
Before 1940	52	2.40	1.09, 5.31	(0.004)	2.13	1.19, 3.83	(0.007)
No. of years worked as a radiologic technologist							
≤10§	49	1.00			1.00		
11–20	43	0.84	0.56, 1.28		0.83	0.55, 1.25	
21–30	27	0.62	0.38, 1.02		0.62	0.38, 1.00	
>30	46	0.78	0.50, 1.24	(0.416)	0.76	0.48, 1.19	(0.330)

* RR, relative risk (stratified for sex, race, attained age, and calendar year of follow-up and adjusted for marital status, body mass index, smoking, alcohol intake, parity, menopausal status, and history of myocardial infarction; subjects with missing data and subjects who had never worked were coded as separate categories with estimates not shown); CI, confidence interval.

† Based on the slope estimate of the continuous variable; parentheses indicate negative slope estimate.

‡ *International Classification of Diseases*, Eighth Revision (ICD-8), codes 390.0–458.9; *International Classification of Diseases*, Ninth Revision (ICD-9), codes 390.0–459.9; 1,070 cases.

§ Baseline category.

¶ ICD-8 and ICD-9 codes 410.0–414.9; 633 cases.

ICD-8 and ICD-9 codes 430.0–438.9; 174 cases.

before 1950. However, levels of exposure may be inferred from historical changes in protection standards and other published information. In 1924, the American Roentgen Ray Society recommended a tolerance dose of one hundredth of an erythema dose per month for radiation workers, which is equivalent to about 0.7 Sv per year (9). Ten years later, the US Advisory Committee on X-ray and Radium Protection proposed the first formal standard of 0.1 roentgen per day (or 0.3 Sv per year, 1 year = 300 workdays) (9). One study estimated that radiologic workers using nonprotective equip-

TABLE 5. Relative risks for mortality by number of years worked in different time periods for the subcohort of certified US radiologic technologists who completed a questionnaire between 1983 and 1990 and were followed from completion of the questionnaire through the end of 1997

Time period	Internal comparison: RR* by the following no. of years worked as a radiologic technologist			Internal comparison: Trend *p*†	External comparison: RR by the following no. of years worked as a radiologic technologist			External comparison: Trend *p*
	0‡	>0–5	>5		0	>0–5	>5	
Diseases of the circulatory system§								
Before 1950	1.00	1.00	1.15	0.007	1.00	0.97	1.06	0.269
1950–1959	1.00	0.93	0.99	(>0.5)	1.00	0.94	0.99	(>0.5)
1960–1969	1.00	0.96	1.05	0.408	1.00	0.90	0.93	(>0.5)
1970 or later	1.00	0.83	0.84	(0.140)	1.00	0.91	0.94	(>0.5)
Ischemic heart disease¶								
Before 1950	1.00	0.95	0.94	>0.5	1.00	0.92	0.86	(0.221)
1950–1959	1.00	0.86	1.10	0.395	1.00	0.92	1.15	0.294
1960–1969	1.00	0.88	0.95	>0.5	1.00	0.83	0.85	(>0.5)
1970 or later	1.00	0.92	0.88	(0.309)	1.00	0.98	0.97	(>0.5)
Cerebrovascular disease#								
Before 1950	1.00	1.48	2.01**	<0.001	1.00	1.39	1.93**	0.001
1950–1959	1.00	1.01	0.89	(>0.5)	1.00	1.04	0.89	(>0.5)
1960–1969	1.00	0.85	0.55**	(0.048)	1.00	0.84	0.55**	(0.045)
1970 or later	1.00	1.17	1.18	>0.5	1.00	1.16	1.18	>0.5

* RR, relative risk (stratified for sex, race, attained age, and calendar year of follow-up and adjusted for marital status, body mass index, smoking, alcohol intake, parity, menopausal status, and history of myocardial infarction). A separate model was fitted for each time period restricted to subjects that were between 15 and 65 years of age at some time during that period. Models were adjusted for years worked in other periods. Subjects with missing data and subjects who had never worked were coded as separate categories with estimates not shown.

† Based on the slope estimate of the continuous variable; parentheses indicate negative slope estimate.

‡ Baseline category.

§ *International Classification of Diseases*, Eighth Revision (ICD-8), codes 390.0–458.9; *International Classification of Diseases*, Ninth Revision (ICD-9), codes 390.0–459.9.

¶ ICD-8 and ICD-9 codes 410.0–414.9.

ICD-8 and ICD-9 codes 430.0–438.9.

** 95% confidence interval excludes 1.0.

ment, that is, machines without shielding of the tube housing and walls, during the period of 1920–1930 could have been exposed to 1 Sv per year (23). A small number of the subjects in the present study worked during this period. The conditions must have improved toward the late 1930s. A 1940 survey of a large number of US hospitals showed that the average exposure ranged from about 0.01 to 0.25 Sv per year, depending upon how well the installations were shielded (24). These levels of exposure may have persisted until late 1950. Thus, in a 1953 survey of the radiologic technologists at the Cleveland Clinic, the usual weekly dose exceeded 0.1 roentgen (0.05 Sv per year, 1 year = 50 work-weeks) but rarely exceeded 0.3 roentgen (0.15 Sv per year) (25). Subgroups of the cohort for which elevated relative risks were found in this study worked during this period. In 1957, the International Commission of Radiological Protection recommended a dose limit of 0.05 Sv per year (9)—a large reduction compared with previous limits. Based on these figures, a cumulative dose of 2 Sv or more is conceivable for a radiologic technologist who started working in 1935 and continued to work during the 1940s and 1950s.

Findings from sensitivity analyses, performed to check the robustness, specificity, and generalizability of our results, included the following: similar results for external and internal comparisons (although we emphasize internal comparisons because standard US population rates may not be an appropriate comparison for worker rates because of a healthy worker bias that can vary with work characteristics (26)); no relation of year first worked or number of years worked with other causes of death presumably unrelated to radiation exposure (including infectious, parasitic, and respiratory diseases or injuries and poisoning); similar results in an extension of our analysis to the entire cohort including nonrespondents and subjects who died before questionnaire administration (although the extended analysis had to be restricted to the only occupational data available, i.e., the year first certified as a radiologic technologist and number of years certified); and similar findings, albeit with wider confidence intervals, in a restriction of the analyses to the subset of workers with complete observations.

Our cohort is one of the few that includes a large number of female workers exposed to chronic low-dose ionizing radiation. Strengths of the study include nationwide representation, nearly complete follow-up, and the availability of individual worker data on lifestyle and other known risk factors for circulatory system diseases. The consistency of the effects of known risk factors for mortality from circulatory system diseases in our study and those from the literature supports the validity of the cause of death information.

A limitation is the lack of information on other known risk factors for circulatory system diseases (including hypertension, diabetes, hypercholesterolemia, and family history of circulatory system diseases). Failure to account for these established important risk factors could introduce confounding bias. However, all analyses were adjusted for body mass index, linked with diabetes, hypercholesterolemia, and hypertension (15, 27). The major weakness is the absence of radiation dose estimates. However, earlier years of first employment were also associated in this cohort with increased risk for breast cancer, a known radiogenic cancer (7). This lends credibility to the use of year first worked as a surrogate measure for radiation exposure. Moreover, increased risk for diseases of the circulatory system was observed several decades after first occupational radiation exposure because the most significant radiation exposures are likely to have occurred in the early years, in agreement with the results for atomic bomb survivors (4).

A number of mechanistic hypotheses have been proposed (28–30). Although based primarily on high radiation doses, they provide some useful insights. Radiation exposure can damage myocardial microvasculature directly (28) or indirectly by forming fibrosis via the effect on the microvasculature (29). Damage to the microvasculature may limit cardiac responsiveness to additional stressors, such as hypertension and subclinical ischemia, over the life span. Further, inflammation and chronic infection may play a significant role in atherogenesis (30), although an association between radiation and inflammation is not established. Epidemiologic insights are needed to help elucidate the possible mechanisms, but data on the association between chronic low-dose radiation and diseases of the circulatory system are currently limited.

ACKNOWLEDGMENTS

This research was supported in part by contracts N01-CP-15673, N01-CP-51016, N02-CP-81005, and N02-CP-81121 by the National Cancer Institute, National Institutes of Health, and the US Public Health Service.

The authors are grateful to the radiologic technologists who participated in this study; Jerry Reid of the American Registry of Radiologic Technologists for continued support of this project; Diane Kampa of the University of Minnesota for data collection and coordination; Kathy Chimes of Westat for data management; Roy Van Dusen of Information Management Services, Inc., for biomedical computing; and Drs. Tamara B. Harris and Jay H. Lubin for helpful advice. They also wish to acknowledge their appreciation to Drs. John Boice, Jr., and Jack Mandel who played a critical role in the initiation, design, and maintenance of this cohort study for many years.

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APPENDIX

The only quantitative risk estimates for circulatory system diseases in relation to ionizing radiation exposures at lower levels than those used in radiotherapy have been provided by the study of atomic bomb survivors, among whom excess relative risks of 0.14 per Sv colon dose have been estimated for heart disease mortality and 0.09 per Sv colon dose for stroke (4). In the absence of individual dose estimates for the radiologic technologists in our study, it is not possible to determine whether the level of relative risks observed in the present study is consistent with the risks seen among the atomic bomb survivors. However, indirect information provides data to assess consistency. In our study, we found relative risks per year worked before 1950 of 1.01 (95 percent CI: 0.98, 1.03) for ischemic heart disease and 1.06 (95 percent CI: 1.03, 1.10) for stroke. Based on the risk estimates from the study on atomic bomb survivors (4), the estimated dose in sieverts per year worked prior to 1950 can be approximated by the ratio of the excess relative risk per year worked prior to 1950 from our data and the excess relative risk per unit dose in sieverts from the study on atomic bomb survivors (4). Therefore, the average yearly estimated dose linked with the relative risks found in our study is $(1.01 - 1.00)/0.14 = 0.07$ Sv for ischemic heart disease and $(1.06 - 1.00)/0.09 = 0.7$ Sv for stroke. The average yearly estimated dose linked with a relative risk for stroke at the lower 95 percent confidence limit is $(1.03 - 1.00)/0.09 = 0.3$ Sv.